Remarks

Reconsideration of this Application is respectfully requested. Claims 62-72, 76 and 77 are pending in the application, with claim 62 being the independent claim. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Rejections Under 35 U.S.C. § 103

A. Claims 62, 64 and 65

The Examiner rejected claims 62, 64 and 65 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pluenneke (U.S. Pub. No. 2001/0021380) in view of Fabrizio *et al.* (EP Pat. No. 0 492 448 A1), Horwitz (Intl. Pub. No. WO 92/22324), Adair *et al.* (EP Pat. No. 0 516 785 B1), and Reza Dana (Intl. Pub. No. WO 00/27421). *See* Office Action at pages 2-5. Applicants respectfully disagree for at least the reasons of record and for the additional reasons that follow.

1. Legal Principles

Obviousness determinations under 35 U.S.C. § 103 are carried out according to the standard set forth by the United States Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 148 USPQ 459 (1966):

> [u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Id. at 17-18, 148 USPQ at 467.

In proceedings before the U.S. Patent and Trademark Office (USPTO), the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). Additionally, there must be a reason or rationale behind an obviousness determination and "this analysis should be made explicit." *See KSR International Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1741 (2007) (citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.").

In response to *KSR*, the USPTO issued "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" 72 Fed. Reg. 195, pp. 57526-35 (October 10, 2007) (hereinafter "2007 *KSR* Guidelines"). The 2007 *KSR* Guidelines reiterate and emphasize the Examiner's role as a fact finder, using the factual inquiries set forth in *Graham*. Based on the fact record, the Examiner must use "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." 2007 *KSR* Guidelines at page 57529 (internal citation omitted).

On September 1, 2010, the USPTO issued "Examination Guidelines Update: Development in the Obviousness Inquiry After *KSR* v. *Teleflex*." 75 Fed. Reg. 169, pp. 53643-60 (hereinafter "2010 *KSR* Guidelines Update"). The 2010 *KSR* Guidelines Update provides reviews of several Federal Circuit cases that have involved the

application of the law of obviousness since *KSR* to assist USPTO patent examiners, as discussed in further detail below.

> ***2. One of ordinary skill would have considered the ability of antibody fragments to penetrate the cornea differently than the ability to penetrate other tissues, such as tumor tissue, because of the physiological differences between the cornea and other tissues.***

At page 3 of the prior Office Action mailed on July 31, 2009, the Examiner alleged that Applicants have not provided:

> sound scientific reasoning or objective evidence *why* one of ordinary skill in the art would have considered the ability of an $F(ab')_2$ antibody to penetrate the cornea any different than the ability of an $F(ab')_2$ antibody to penetrate any other tissue, e.g., tumor tissue.

(emphasis in original).

Applicants assert that such evidence is available, as discussed in the Amendment and Reply filed on November 2, 2009 and for the additional reasons that follow. At pages 3-4 of the present Office Action, the Examiner indicated that the evidence in Exhibits B-E of the Amendment and Reply filed on November 2, 2009 was not persuasive because only the abstracts of the references were provided. In response, Applicants submit herewith replacement Exhibits B-E providing the full-length articles corresponding to the abstracts submitted as Exhibits B-E in the Amendment and Reply filed on November 2, 2009. Applicants assert these articles provide the sound scientific reasoning and objective evidence the Examiner alleges has not been provided as to why one of ordinary skill in the art would have considered the ability of an $F(ab')_2$ antibody to penetrate the cornea any different than the ability of an $F(ab')_2$ antibody to penetrate any other tissue, such as tumor tissue.

The cornea is the front part of the eye that covers the iris, pupil and anterior chamber. *See, e.g.,* page 7 of the Amendment and Reply filed on February 17, 2009. The cornea contains five specialized layers, including Bowman's layer and Descemet's membrane, two barrier layers containing collagen. *See id.* Unlike many other types of tissues, the cornea does not contain blood vessels. *See, e.g.,* Zhu *et al., J. Interferon Cytokine Res. 19*:661-669; 1999 at page 661 (document NPL31 of the Information Disclosure Statement dated March 16, 2007; copy also provided as Exhibit A of the Amendment and Reply filed on November 2, 2009).

In the Amendment and Reply filed on November 2, 2009, Applicants submitted Exhibit B (Sasaki, H., *et al., Crit. Rev. Ther. Drug Carrier Syst., 16*:85-146; 1999) in support of the proposition that one of ordinary skill in the art would understand that systemically administered drugs would have poor access to the cornea because of the lack of blood flow and barrier layers associated with the corneal structure. More specifically, Exhibit B provides that

> ...the eye is protected by a series of complex defense mechanisms. From a therapeutic standpoint, these defense mechanisms make it difficult to achieve an effective concentration of drug within the target area in the eye. Systemically administered drugs have poor access because of the blood-aqueous barrier, which prevents drugs from entering into the aqueous humor, and the blood-retinal barrier, which prevents drugs from entering into the extravascular space of the retina and into the vitreous body.

Exhibit B at page 86.

Topical administration can be an alterative to systemic administration. However, one of ordinary skill in the art would have understood at the time the present application was filed that the cornea is an effective barrier to topical penetration because the corneal

epithelium has annular tight junctions which surround the corneal epithelium. For example, Exhibit B provides that:

> [t]he cornea prevents drug penetration by means of a trilaminate structure consisting of a hydrophilic stromal layer sandwiched between a very lipophilic epithelial layer and a much less lipophilic endothelial layer.

Exhibit B at page 90.

Exhibit B also provides that:

> ...horseradish peroxidase permeation through the cornea stopped within the top two to three epithelial cell layers due to tight junctions between the cells. These tight junctions are the main barrier to the transepithelial penetration of ions and neutral molecules through the paracellular pathway.

Exhibit B at page 118 and Figure 12.

Additionally, one of ordinary skill would have understood that topically applied drugs are rapidly eliminated from the precorneal area. In this regard, Exhibit B provides that:

> [t]he elimination of drug in the precorneal area is important for determining the ocular bioavailability and systemic side effect. The loss of drug from the precorneal area is a net effect of the drainage, tear turnover, noncorneal absorption, and corneal absorption-rate processes. The drainage rate is much faster than the corneal adsorption rate, with the result that most of the topically applied drug is eliminated from the precorneal area within 90 seconds.

Exhibit B at page 88.

Therefore, Exhibit B clearly supports Applicants' contentions that one of ordinary skill in the art would understand that systemically administered drugs would have poor access to the cornea.

In the Amendment and Reply filed on November 2, 2009, Applicants submitted Exhibits C-E for the proposition that one of ordinary skill in the art would have understood at the time the present application was filed that the penetration of therapeutic agents into tumor tissue is different than the penetration of therapeutic agents into non-tumor tissue (*e.g.,* cornea tissue) because of the differences between tumor physiology compared to normal tissue. More specifically, Exhibits C-E provide that tumor physiology has significant influence on the sensitivity to anti-cancer drugs, including antibodies. For example, Exhibit C (Tannock, I.F., *Cancer Metastasis Rev., 20*:123-132, 2001) provides that the rate of cellular proliferation is heterogeneous within solid tumors and decreases with increasing distance from tumor blood vessels. *See* Exhibit C at page 124, left column. Because anti-cancer drugs are more active against dividing cells, slowly proliferating cells of the tumor tend to be spared from the effects of anti-cancer drugs. *See id.* Exhibit C also provides that conditions associated with the microenvironment of tumors such as hypoxia, low pH, poor blood supply, cellular contact and high cell concentration, also effect overall tumor sensitivity to anti-cancer drugs. *See, e.g.*, Exhibit C at pages 124-125.

Additionally, Exhibit D (Jain, R.K., *Cancer Metastasis Rev., 9*:253-266, 1990) indicates that a key problem with the treatment of cancer with therapeutic agents such as monoclonal antibodies is the inability of the agent to reach the target in an adequate quantity. *See, e.g.*, Exhibit D at Abstract and page 254, left column. More specifically, three physiological factors of tumors are identified as responsible for the poor localization of such agents: (1) heterogeneous blood supply; (2) elevated interstitial pressure; and (3) large transport distances through the interstitial spaces of a tumor. *See, e.g.*, Exhibit D at pages 254, 257 and 258.

Exhibit E (Jain, R.K., *Annu. Rev. Biomed. Eng., 1*:241-263, 1999) provides further support regarding the significant influence of tumor physiology on the sensitivity to anti-cancer drugs. In particular, Exhibit E provides that the "chaotic" blood supply of a tumor is the first barrier encountered by blood-borne therapeutic agents. *See, e.g.*, Exhibit E at page 243. In addition to a heterogeneous blood supply, Exhibit E provides that the elevated pressure and large transport distances within the interstitium of tumors also result in a non-uniform uptake of therapeutic agents. *See, e.g.*, Exhibit E at pages 244 and 247-248.

As such, one of ordinary skill in the art would have considered the ability of a therapeutic agent such as a $F(ab')_2$ antibody to penetrate the cornea differently than a tumor because of the differences in tumor physiology compared to non-tumor tissue. Thus, one of ordinary skill in the art would not have necessarily expected that the improved penetration of $F(ab')_2$ fragments into tumor tissue disclosed in Horwitz would apply to the penetration of $F(ab')_2$ fragments into non-tumor tissues such as cornea tissue.

Taken together, one of ordinary skill at the time the present application was filed would have understood the ability of therapeutic agents, such as antibody fragments, to penetrate the cornea differently than the ability of agents to penetrate other tissues such as tumor tissue, because of the physiological and structural barriers of the cornea to the systemic and topical administration of agents. Accordingly, Applicants maintain that the evidence of record supports the conclusion that it was not predictable that $F(ab')_2$ antibody fragments would better penetrate the cornea even if the fragments might better penetrate other tissues such as tumor tissue.

For at least these reasons, Applicants maintain that the Examiner has not met the criteria required to establish a *prima facie* case of obviousness of claim 62. Claims 64

and 65 depend indirectly and directly on claim 62, respectively. Applicants respectfully assert that claims 64 and 65 are allowable for at least the same reasons set forth above regarding claim 62, and further in view of their own respective distinguishing features. *See* MPEP § 2143.03, citing *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) ("If an independent claim is nonobvious under 35 U.S.C. § 103, then any dependent claim depending therefore is nonobvious.").

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 62, 64 and 65.

3. Even if prima facie obviousness were established, evidence of unexpected results exists which would overcome such a rejection.

Secondary considerations of non-obviousness include unexpected results. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 694, 148 USPQ 459, 467 (1966). The Federal Circuit has recently reaffirmed that the USPTO must in all cases consider any evidence tending to support secondary considerations of non-obviousness. *In re John B. Sullivan and Findlay E. Russell*, 498 F.3d 1345 (Fed. Cir. 2007). As discussed above, the Examiner has not established a *prima facie* case of obviousness with respect to the claims. Moreover, the record demonstrates that *prima facie* obviousness, even if it were established, would be negated by the unexpected and superior properties of the claimed subject matter.

As evidence in support of the non-obviousness of the claimed subject matter, Applicants provided the Declaration of Dr. Jorge F. Paniagua-Solís as Exhibit F to the Amendment and Reply filed on November 2, 2009. At page 5 of the present Office Action, the Examiner contends that the Dr. Paniagua-Solís' Declaration is not convincing

because Dr. Paniagua-Solís makes no case why he found these results to be unexpected. Applicants respectfully disagree.

As provided in the Declaration, Dr. Paniagua-Solís is the Director de Invesigación at Laboratorios Silanes and Instituto Bioclon in México, D.F. Dr. Paniagua-Solís received a master's degree in Biomedical Sciences and Immunology in 1990 and a doctorate degree in Biomedical Sciences and Immunology in 1996 from the School of Medicine of the Universidad Nacional Autónoma de México. *See, e.g.*, page 2 of Dr. Paniagua-Solís' curriculum vitae attached to the Declaration. Dr. Paniagua-Solís has laboratory experience in immunochemistry dating back to at least 1981 (*see, e.g.*, page 2), has published an extensive list of journal articles, books and book chapters related to antibodies and immunology (*see, e.g.*, pages 3-13), and is an inventor of several patents and patent applications related to antibodies and ophthalmic preparations (*see, e.g.*, pages 11-12). In view of his curriculum vitae, it is clear that Dr. Paniagua-Solís was an active and experienced researcher in immunology at the time the present application was filed and therefore would be considered a person of at least ordinary skill in the art. (Applicants note the present application is the U.S. national stage of International Appl. No. PCT/IB2003/002971, filed on July 25, 2003.) The Examiner has not provided any reason why Dr. Paniagua-Solís would not be considered a person of ordinary skill in the art.

According to the USPTO's training materials, a Declaration Under 37 C.F.R. § 1.132 can include statements in the form of an opinion, such as a "statement expressing what the declarant thinks, believes, or infers with regard to certain facts." *See* page 12 of the OPLA *KSR* Training Materials Titled "37 CFR § 1.132 Practice," posted May 9, 2008, available at http://www.uspto.gov/web/offices/pac/dapp/opla/ksr/ksr_132

declarations. ppt. In the Declaration, Dr. Paniagua-Solís indicates he understands the subject matter of the present claims and has reviewed the references cited in the Office Action mailed July 31, 2009. *See* Declaration at paragraphs 4-5. In particular, Dr. Paniagua-Solís states that *none* of the references cited by the Examiner provide experimental evidence for the effectiveness of anti-TNFα $F(ab')_2$ fragments in the treatment of corneal transplant. Dr. Paniagua-Solís then explains in the Declaration the experiments he supervised that provide such evidence. More specifically, Dr. Paniagua-Solís' Declaration provides data showing that treatment with anti-TNFα $F(ab')_2$ fragments significantly and unexpectedly increases graft cornea survival (*see* Figure 1) and decreases the morphological properties of the cornea associated with graft rejection (*see* Figure 2). Dr. Paniagua-Solís concludes the increased graft cornea survival and decreased morphological properties of the cornea associated with graft rejection would not have been expected in view of the art cited by the Examiner. *See, e.g.*, Declaration at paragraph 11.

As such, in view of Dr. Paniagua-Solís' statements that he had considered the cited references and found none of the cited references provide the experimental results which are then provided the Declaration, Applicants disagree that Dr. Paniagua-Solís has not provided a reason why he found the experimental results unexpected or why the art would have found the results unexpected. Rather, these statements by Dr. Paniagua-Solís provide a basis for his opinion that the evidence is unexpected, and therefore Dr. Paniagua-Solís' opinion is appropriate evidence under 37 C.F.R. § 1.132 that should be given due consideration.

Therefore, even if a *prima facie* case of obviousness were established, which it has not, Applicants respectfully contend that these unexpected results would be sufficient to overcome such a rejection.

At page 5 of the Office Action, the Examiner appears to acknowledge Dr. Paniagua-Solís' opinion, but indicates that the evidence of non-obviousness does not outweigh the evidence of obviousness in view of the teachings in the cited art. Even if such evidence of obviousness were present, Applicants submit that the evidence of non-obviousness previously of record, along with the additional evidence of non-obviousness presented herein, is significant enough to establish the non-obviousness of the claimed invention in view of recent USPTO guidance and Federal Circuit case law.

i. A nexus exists between the evidence of secondary considerations and the claimed invention.

According to MPEP § 716.01(b), any secondary evidence must be related to the claimed invention. To be given substantial weight, evidence of secondary considerations of non-obviousness must be relevant to the subject matter as claimed, and therefore the Examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 305 n.42 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). Because the evidence of unexpected results is specifically directed to the effects of topically administering anti-TNFα $F(ab')_2$ fragments directly to eye to prevent rejection in cornea transplant, a sufficient connection between the objective evidence of non-obviousness and the claimed invention is clearly established. As such, the evidence of nonobviousness of record is of probative value in the determination of non-obviousness of the claimed invention and should be given substantial weight. *See*

also Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387 (Fed. Cir. 1988), *cert. denied*, 488 U.S. 956 (1988).

ii. The evidence of secondary considerations is commensurate in scope with the claimed invention.

Whether unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support. MPEP § 716.02(d). Because the evidence of unexpected results is specifically directed to the effects of topically administering anti-TNFα $F(ab')_2$ fragments directly to eye to prevent rejection in cornea transplant, it is clearly within and commensurate in the scope of the claimed invention. Thus, this evidence of non-obviousness should be given substantial weight.

iii. 2010 KSR Guidelines Update

As mentioned above, the USPTO recently issued "Examination Guidelines Update: Development in the Obviousness Inquiry After *KSR* v. *Teleflex*" to assist USPTO patent examiners with application of the law of obviousness since *KSR* and address evidence of non-obviousness, such as unexpected results and commercial success evidence. 75 Fed. Reg. 169, pp. 53643-60 (hereinafter "2010 *KSR* Guidelines Update"). In general, the 2010 *KSR* Guidelines Update emphasizes the importance of considering rebuttal evidence of non-obviousness submitted. *Id.* at 53644 and 53657. Once rebuttal evidence has been presented, USPTO personnel should reconsider any initial obviousness determination in view of the entire record and should not summarily dismiss rebuttal evidence as not compelling or insufficient. *Id.* at 53657. Moreover, an obviousness rejection should be made or maintained only if evidence of obviousness

outweighs evidence of non-obviousness. *Id.* at 53658, referencing MPEP § 706(I) ("The standard to be applied in all cases is the 'preponderance of the evidence' test. In other words, an examiner should reject a claim if, in view of the prior art and evidence of record, it is more likely than not that the claim is unpatentable."). Based on this guidance, Applicants contend that the significance of the rebuttal evidence of record, the clear nexus between the claimed invention and the rebuttal evidence, and the commensurate scope of the evidence in view of the claimed invention, would outweigh any alleged *prima facie* case of obviousness.

Thus, even if a *prima facie* case of obviousness were established, which it has not, Applicants respectfully assert that these unexpected results would be sufficient to overcome such a rejection. For at least these reasons, Applicants respectfully request this rejection be withdrawn.

B. Claim 63

The Examiner rejected claim 63 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pluenneke in view of Fabrizio *et al.*, Horwitz, Adair *et al.*, Looareeswan *et al.* (*Am. J. Trop Med. Hyg.* 61:26-33, 1999) and Reza Dana. *See* Office Action at page 5. Claim 63 depends from claim 62. Therefore, Applicants assert that claim 63 is also allowable for at least the reasons set forth above regarding claim 62, and respectfully request reconsideration and withdrawal of the rejection.

C. Claims 66-72, 76 and 77

The Examiner rejected claims 66-72, 76 and 77 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pluenneke in view of Fabrizio *et al.*, Horwitz, Adair *et al.*, Looareeswan *et al.*, and Reza Dana as applied to claims 62, 64 and 65, and in further

view of the Merck Manual of Diagnosis and Therapy (Mark Beers and Robert Berkow eds., Published by Merck Research Laboratories, 17th ed., 1999, pages 722-24) and DeVries (U.S. Appl. Pub. No. 2003/0180294). *See* Office Action at pages 5-7. Claims 66-72, 76 and 77 depend either directly or indirectly from claim 62. Thus, Applicants assert that claims 66-72, 76 and 77 are allowable for at least the reasons set forth above regarding claim 62, and further in view of their own respective distinguishing features. *See* MPEP § 2143.03, citing *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) ("If an independent claim is nonobvious under 35 U.S.C. § 103, then any dependent claim depending therefore is nonobvious.").

D. Claims 66-68

The above notwithstanding, the combination of the cited references do not teach or suggest the administration times specified in any one of claims 66-68. The Supreme Court has recently stated that "[w]hen there is a design need or market pressure to solve a problem and there are a *finite number* of identified, *predictable* solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.... [i]n that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *See KSR* at 17 (emphasis added). Also, the Federal Circuit has stated that "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

In this instance, the cited references at best provide an extremely large number of potential options upon which one of ordinary skill in the art could combine to arrive at the claimed methods having the specified administration times following corneal

transplant. While the Examiner may hone in on a particular composition and administration time following corneal transplant using the claimed methods as a starting point, this is applying hindsight reasoning in selecting which particular composition and which administration time, of the numerous possible options to use as a starting point. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); and *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991) (stating it was impermissible to use applicant's structure as a template to select elements from a reference or references to fill in the gaps).

Therefore, for at least these reasons, Applicants assert that at least the subject matter of claims 66-68 is allowable and respectfully request that the Examiner reconsider and withdraw the obviousness rejection of at least claims 66-68.

E. Claims 69 and 70

The above notwithstanding, the cited references do not teach or suggest the administration regimens of claim 69 or 70 (*i.e.*, administration at least 3 times a day for about 8 weeks, or about every 10 to 12 hours for about 8 weeks, respectively).

As explained above, Applicants assert that the claimed methods are different from, and have unexpected advantages over other administration regimens that the Examiner alleges are taught by the cited references. For example, as discussed in the Declaration of Dr. Paniagua-Solís, the treatment of mice following cornea grafting with anti-TNFα $F(ab')_2$ fragments three times a day for 8 weeks resulted in significantly and unexpectedly increased graft corneal survival and decreased morphological properties associated with graft rejection. *See, e.g.*, Exhibit F at paragraphs 9-10. As such,

evidence that the claimed methods have significant and unexpected advantages over the compositions the Examiner alleges are taught by the cited art is available.

In addition, as explained above with regard to claims 66-68, the cited references at best provide an extremely large number of potential options upon which one of ordinary skill in the art could combine to arrive at the claimed methods having the specified administration times and administration duration following corneal transplant. While the Examiner may hone in on a particular composition, administration time and administration duration following corneal transplant using the claimed methods as a starting point, this is applying hindsight reasoning in selecting which particular composition and method, of the numerous possible options to use as a starting point.

Therefore, Applicants assert that at least the subject matter of claims 69 and 70 is allowable and respectfully request that the Examiner reconsider and withdraw the obviousness rejection of at least claims 69 and 70.

F. Claims 71, 72, 76 and 77

The above notwithstanding, the cited references do not teach or suggest the administration vehicle of any one of claims 71, 72, 76 and 77 or the specified amount of anti-TNFα $F(ab')_2$ neutralizing antibody fragment in any one of claims 72, 76 and 77.

As explained above, Applicants assert that the claimed methods are different from, and have unexpected advantages over other administration regimens that the Examiner alleges are taught by the cited references. For example, as discussed in the Declaration of Dr. Paniagua-Solís, the treatment of mice following cornea grafting with the eye drop formulations containing propylene glycol and anti-TNFα $F(ab')_2$ fragments at concentrations of 0.01-50 mg/mL (*see* Attachment to Exhibit F) resulted in

significantly and unexpectedly increased graft corneal survival and decreased morphological properties associated with graft rejection. *See, e.g.*, Exhibit F at paragraphs 9-10. As such, evidence that the claimed methods have significant and unexpected advantages over the compositions the Examiner alleges are taught by the cited art is available.

In addition, as explained above with regard to claims 66-68, the cited references, at best, provide an extremely large number of potential options upon which one of ordinary skill in the art could combine to arrive at the claimed methods having the specified administration vehicles and dosages following corneal transplant. While the Examiner may hone in on a particular composition, administration vehicle and administration dosage following corneal transplant using the claimed methods as a starting point, this is applying hindsight reasoning in selecting which particular composition and method, of the numerous possible options to use as a starting point.

Accordingly, Applicants assert that at least the subject matter of claims 71, 72, 76 and 77 is allowable and respectfully request that the Examiner reconsider and withdraw the obviousness rejection of at least claims 71, 72, 76 and 77.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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